

# Medulloepithelioma (diktyoma)

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**SUMMARY** Sixteen cases of medulloepithelioma are described. Clinical data and follow-up were available on 15. Four patients underwent iridocyclectomy initially; all later needed enucleation and one had an orbital recurrence. The remaining 12 patients underwent primary enucleation. All 15 patients with follow-up are alive with no evidence of tumour recurrence. It is suggested that enucleation be performed for all but the most localised tumour. Rubeosis was noted in 13 of the 16 eyes, and this may assist in making the diagnosis. The World Health Organisation histological classification of medulloepithelioma was applied, but some problems were encountered, particularly where the presence of heteroplastic brain tissue was used as a criterion for teratoid tumour and where rosettes were used as a criterion for malignancy.

Medulloepithelioma is an uncommon tumour which arises from undifferentiated non-pigmented ciliary epithelium and which usually presents in childhood. Very rarely it may arise in optic nerve or retina. The tumour is pleomorphic and diagnosis is often delayed.

The tumour usually grows slowly and may be locally malignant. Distant metastasis is uncommon and has been described only in cases where orbital spread has occurred. Broughton and Zimmerman<sup>1</sup> have contributed most to the current understanding of the clinical spectrum and histological classification of the disorder. They reviewed 56 cases derived from the records of the Armed Forces Institute of Pathology (AFIP). Clinical follow-up data were available on 33 of them. Andersen<sup>2</sup> reported a series of 23 cases, about half of which were on record at the AFIP. Reese<sup>3</sup> and Shields<sup>4</sup> have reviewed the subject. Most other publications on medulloepitheliomas comprise single case reports with or without a review of the literature.

This paper presents the histological features of 16 cases of the tumour on record at the Institute of Ophthalmology in London. Clinical data and follow-up information were available on 15 patients. Only two of these patients have previously been the subject of case reports.<sup>5,6</sup>

## Patients and methods

Over 25 years there have been 16 cases of histologic-

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ally confirmed medulloepithelioma in humans on file at the Institute of Ophthalmology for which complete biographical data are available. For the purposes of this study all tissue specimens were reviewed and fresh slides made as appropriate. Attending clinicians and pathologists were contacted for further details and current follow-up status. All but one case has been treated within the United Kingdom.

Pertinent biographical data are presented in Table 1. There were nine females and seven males. The ages at diagnosis ranged from 6 weeks to 48 years and the follow-up from three months to 25 years.

## Results

### CLINICAL FEATURES

The presenting symptoms are detailed in Table 2 and the pretreatment signs in Table 3. The surgical management and histological classification of the surgical specimens are recorded in Table 1. Twelve cases had primary enucleation and all were alive without clinical tumour recurrence. Three of these had extrascleral extension of the tumour, one of whom received adjuvant radiotherapy. These three patients have been followed for between 5 and 11 years.

Four patients initially had iridocyclectomies, either in order to make the diagnosis or in an attempt to excise the tumour. All four have since required enucleation—two for recurrent intraocular tumour, one for reduced vision and pain, and one for rubeotic glaucoma. One of these patients, with persistent intraocular tumour, had recurrent tumour in the

Table 1 *Biographical data, management, and histological classification*

Number	Age at diagnosis	Sex M/F	Follow-up duration	Management	Histology
1	3 yr	M	25 yr	Enucleation	NT B
2	14 yr	F	18 yr	Enucleation	NT B
3	48 yr	M		Enucleation	T B
4	2 yr	M	13 yr	Enucleation	T B
5	11 mth	F	11 yr	Enucleation	NT B
6	8 mth	F	11 yr	Enucleation	NT M (invasive)
7	1 yr	M	13 yr	Iridocyclectomy Enucleation Exenteration + DXT	T M (neuroblastoma)
8	2 yr	F	13 yr	Iridocyclectomy Enucleation	NT M (invasive)
9	6 mth	F	11 yr	Iridocyclectomy Enucleation	NT M (astrocytoma)
10	13 yr	F	12 yr	Enucleation	NT B
11	6 wk	M	5 yr	Enucleation	T M (invasive)
12	14 yr	F	5 yr	Enucleation	NT B
13	10 yr	M	2 yr	Enucleation	T B
14	5 mth	M	5 yr	Enucleation DXT	T M (neuroblastoma, embryonal sarcoma)
15	2.5 yr	F	6 mth	Iridocyclectomy Enucleation	T B
16	4 yr	F	3 mth	Enucleation	T B

T=teratoid. NT=non-teratoid. B=benign. M=malignant.

orbit two years after enucleation. This was treated with exenteration and radiotherapy. The patient had no further clinical metastasis after 11 years. The other three all had tumour cells at the site of the previous surgical section when the whole eye was examined, but the patients have remained clinically free of tumour. Two have been followed up for 11 years and one for six months.

**HISTOLOGICAL FEATURES**

Sixteen cases were reviewed. Ten were benign, of

which seven were non-teratoid. Of the six malignant cases two were aggressively invasive preoperatively. Both were non-teratoid. The teratoid elements found included cartilage in three, and brain (neurones and glia) in two. Some unusual, but not teratoid, elements were also found—angioma in one and ganglion cells in another. No rhabdomyoblasts were found in any of the 16 cases. Most tumours contained rosettes of various types. Cystic change with accumulation of mucopolysaccharide material was seen in three cases. Unequivocal cytologically malignant areas contained neuroblastoma-like tissue in two, embryonal sarcoma-like tumour in one, and astrocytoma in one. Calcification was present in four cases.

**Discussion**

Medulloepithelioma was first recognised and termed ‘carcinome primitif’ by Badel and Lagrange in 1892.<sup>7</sup> Verhoeff described another case in 1904.<sup>8</sup> He gave it the name ‘teratoneuroma’, although his case contained no teratoid elements. Fuchs reported an example in 1908<sup>9</sup> in which the predominant histological feature was a net-like pattern of poorly differentiated cell ribbons, and he used the term ‘diktyoma’ derived from the Greek root for ‘net’. This name makes up in brevity what it lacks in its description of cytological or embryological features, and for years was the most popular term for this tumour. The term ‘medulloepithelioma’ was first applied in 1931 by Grinker.<sup>10</sup> The etymology of these various terms has been discussed elsewhere.<sup>1</sup>

**PATHOLOGY**

Quite recently the classification of tumours arising

Table 2 *Presenting symptoms*

Symptom	No. of patients
Anterior chamber/iris mass	6
Reduced vision	4
Photophobia/epiphora	2
Leukocoria	1
Abnormal pupil	1
Enlarging globe/exophthalmos	2
Heterochromia	1
Squint	1

Table 3 *Pretreatment signs*

Sign	No. of patients
Cataract	8
Rubeosis	13
Glaucoma	8
Anterior chamber/iris mass	6
Retinal mass	2
Squint	1
Enlarged globe	1
Exophthalmos	1
Iritis	1
Retinal detachment	2
Incidental finding — traumatic ruptured globe	1

from the ciliary epithelium has been simplified, largely through the efforts of Zimmerman. His classification has been adopted by the World Health Organisation.<sup>11</sup> Tumours of the ciliary epithelium are divided into congenital (arising from undifferentiated epithelium and presenting commonly in childhood) and acquired (arising from differentiated epithelium and presenting commonly in adults). Undifferentiated cells do not normally persist in the ciliary epithelium into adulthood. All congenital ciliary epithelial tumours are medulloepitheliomas. The acquired group includes hyperplasias, adenomas, and adenocarcinomas.

The diagnosis of medulloepithelioma of the ciliary body is not usually difficult histologically, but classification into the simple and elegant categories of Broughton and Zimmerman<sup>1</sup> may prove harder. The classification splits the tumours into benign and malignant on the basis of cytological features and invasive, rather than metastatic, properties. The latter is not a contentious issue, since these tumours are often locally aggressive and may spread to involve the orbit as well as other intraocular structures. The former set of criteria, involving pleomorphism, mitotic rate, and degree of undifferentiation, are less easy to apply, since these tumours are by definition immature and may be growing quickly. Sheets of basophilic cells may resemble neuroblastoma or undifferentiated retinoblastoma in otherwise unremarkable tumours. Rosetting is not necessarily a helpful diagnostic feature, since 81% of cases in the present series had rosettes, some of the more primitive retinal anlage type, others more like Homer-Wright rosettes, and others with clearly delineated external limiting membranes around a central lumen, resembling Flexner-Wintersteiner rosettes. Occasionally the rosettes have turned 'inside-out', and both of the latter types of rosettes resembled those seen in dysplastic retinas, especially those associated with trisomy 13-15.

It is interesting that heteroplastic cartilage is also associated with this trisomy and with some microphthalmic eyes. This is the most easily recognised heteroplastic or teratoid element. In the present series only two tumours had mature cartilage. Recognition of genuinely teratoid elements can be difficult. In several of our cases areas which appeared to be 'brain' were in fact composed only of glial elements, many showing the well described spongioblastic change, while some appeared gemistocytic. Unequivocal neurone cell bodies were rare but were seen in two cases. We did not regard ganglion cells as being teratoid. Other glial concomitants such as Rosenthal fibres were seen, and one tumour contained frank astrocytomatous areas. Rhabdomyoblasts were seen in one specimen at the Institute of

Ophthalmology from a patient on whom biographical data were not available, but not in any of the 16 documented cases reported here.

These tumours present a spectrum of malignancy. While most behave well, without overt aggressive invasion, the AFIP series included four deaths from tumour.

#### CLINICAL FEATURES

Rubeosis was a clinical or histological feature of 13 of the 16 cases in this study, as compared with only 11 of 56 cases in the AFIP series. It may be a useful confirmatory sign when making the diagnosis. We know of no work on angiogenic factors in these tumours.

The life expectancy of treated patients is very good. In the present series all 15 patients with follow-up are alive, with no evidence of residual tumour. All affected eyes had been removed, however. In the AFIP series the presence of orbital involvement was a major determinant of survival,<sup>1</sup> though the present series includes survivors even with extrascleral extension of tumours containing cytological evidence of malignancy.

The best treatment for these patients is uncertain. The tumour is too uncommon for any one centre to have acquired much experience in different therapeutic strategies. Broughton and Zimmerman suggest that local excision be attempted for small, well circumscribed tumours. They base this recommendation on two patients who had had excision iridocyclectomies with no apparent tumour recurrence after a follow-up of between 1 and 22 years. The age of the patients at treatment is not given, nor is their subsequent visual function or the presence of cataract, rubeosis, glaucoma, or squint. Given the usual onset of these tumours in early childhood, one might anticipate that such surgery would result in significant amblyopia. Furthermore, it is not clear whether complete excision of the tumours was achieved: the possibility of corneoscleral extension, which is one of the criteria of malignancy, may have been difficult to exclude.

In the same series, eight eyes which had undergone iridectomy or iridocyclectomy as an initial procedure required later enucleation, making the overall chance of retaining the eye after such surgery 20%. The tumour is typically friable and difficult to manipulate surgically. Although about one-half of the tumours contain melanin pigment microscopically,<sup>1</sup> they are often not clinically pigmented. This makes definition of the posterior extent of the tumour by transillumination more difficult. The attendant rubeosis increases the risk of perioperative intraocular haemorrhage.

Broughton and Zimmerman<sup>1</sup> remarked on the

frequency with which highly malignant looking areas within the tumour appeared to be confined by benign tumour, and they considered that this might retard the clinical expression of malignancy. Surgical manipulation might adversely affect such a balance. The prognosis for tumours confined within the globe is uniformly excellent: no case of tumour death has been recorded without evidence of orbital involvement.

All these factors militate against attempting local excision of all but the most circumscribed tumours, given the limited chance of anatomical and functional success of the operation and the potential for promoting orbital recurrence.

We know of no data on the treatment of ocular medulloepithelioma by radiotherapy, though the central nervous system counterpart of the tumour is known to be radiosensitive. While it would be technically feasible to treat ocular medulloepithelioma by local radiotherapy employing a radioactive scleral plaque or a proton beam, the rarity of the tumour and the difficulty in establishing the diagnosis clinically would suggest that a pretreatment tissue diagnosis would be required for the proper assessment of the approach. The potential hazard of intraocular biopsy of a locally aggressive tumour and the difficulty of obtaining a tissue sample representative of the entire tumour would also hamper the investigation of this option.

We recommend that enucleation should be the primary treatment for most cases. Where a credible non-neoplastic differential diagnosis exists, incisional biopsy may be considered with a view to

subsequent radiotherapy for localised tumours and enucleation for extensive tumours.

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